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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/754,775 | 01/04/2001 | David J. Grainger | 295.009US3 | 6351 |

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| EXAMINER | |
|---|---|
| KIM, JENNIFER M | |
| ART UNIT | PAPER NUMBER |
| 1628 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 02/07/2011 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

uspto@slwip.com
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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/754,775 | GRAINGER ET AL. | |
| | Examiner | Art Unit | |
| | JENNIFER M. KIM | 1628 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *173-177,179-194,196-200,202,203,205,206,231 and 234* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *173-177,179-194,196-200,202,203,205,206,231 and 234* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/17/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The amendment filed November 4, 2010 have been received and entered into the application.

### Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 183 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 183 recites the limitation "the increase in TGF-beta" in line 1. There is insufficient antecedent basis for this limitation in the claim.

### Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 173-177, 179-194, 196-200, 202,203, 205 and 206 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 153, 154, 157-165, 169-175, 182, 185 and 186 of copending Application No. 10/729,056. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending Application teaches an aspect of the claims in the instant application. For example, the method of claims 173-177, 179-194, 196-200, 202,203, 205 and 206 in the present application is similar to the method claimed in claims 153, 154, 157-165, 169-175, 182, 185 and 186 utilizing same biological pathway comprising increasing the level of TGF-beta encompassing utilized same active agents. The copending application teaches the mechanisms of action or biological pathways presently claimed by Applicants and renders obvious the diseased claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 173-177, 179-194, 196-200, 202-203, 205 and 206 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 1-16 of U.S. Patent No. 5,847,007 of record in view of Chander et al. (1991) of record.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent disclose and teach an aspect of the claims in the present application. Both sets of claims encompass administration of the same active agent (a structural analog of tamoxifen) to the same subject (a mammal afflicted with a cardiovascular or vascular indication such as atherosclerosis) for purpose of increasing TGF-beta level. The patent does not expressly teach the specific tamoxifen analog (i.e. idoxifene), however, the employment of a structural analog of tamoxifen such as idoxifene would have been obvious variations of the other to one of ordinary skill in the art since it is well known in view Chander et al. that idoxifene (pyrrolidino-4-iodotomoxifen) is a new analogue of tamoxifen (see title).

Claims 173-177, 179-194, 196-200, 202-203, 205 and 206 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4 of U.S. Patent No. 5,773,479. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating atherosclerosis condition in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the patent and

hence renders obvious over the disease and the agents claimed in the patent. The patent do not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 173-177, 179-194, 196-200, 202-203, 205 and 206 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-10 of U.S. Patent No. 6,166,090. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating atherosclerosis in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the patent and hence renders obvious over the disease and the agents claimed in the patent. The patent does not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 173-177, 179-194, 196-200, 202-203, 205 and 206 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, 19, 27, 30-37, 38, 39, 41, 42 of U.S. Patent No. 6,251,920. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of treating a condition selected from atherosclerosis, stroke, thrombosis, myocardial infarction condition in a mammal comprising administering structural analogs of tamoxifen. The instant application teaches the method of treatment of vascular indication administering the therapeutic agents claimed by Applicants in the patent and hence renders obvious over the disease and the agents claimed in the patent. The patent does not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

Claims 173-177, 179-194, 196-200, 202-203, 205 and 206 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 17 of U.S. Patent No. 6,262,079 Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches an aspect of the claims in the instant application. For example, the instant application and the co-pending application teach a method of inhibiting vascular smooth

muscle cell proliferation in a mammal comprising administering structural analogs of tamoxifen. The instant application is towards the method of inhibiting smooth muscle cells administering the therapeutic agents claimed by Applicants in the patent and hence renders obvious over the disease and the agents claimed in the patent. The patent does not explicitly teach using a sustained release dosage form of structural analog of tamoxifen. The pharmaceutical forms, e.g., sustained release, immediate release etc; mode of administration etc are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.

**Claim Rejections - 35 USC § 103**

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 173-177, 179-194, 196-200, 202, 203, 205, 206, 231 and 234 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grainger et al. (WO 94/26303) of record in view of Chander et al. of record, Sachs et al. (U.S.Patent No. 5,436,243), Hasmann et al (1994), and Frank (1991) of record.

Grainger et al. teach that tamoxifen as well as its functional equivalents, analogs or derivatives thereof are a preferred TGF-beta activator/production stimulator. (page 4, lines 1-5). Grainger et al. teach that these TGF-beta activators and TGF-beta production stimulators are employed to maintain or increase vessel lumen diameter in a diseased or injured vessel of a mammal. (abstract). Grainger et al. teach that TGF-

beta activators are useful in patients at a high risk of developing atherosclerosis or with signs of hypertension resulting from atherosclerotic changes in vessels or vessel stenosis due to hypertrophy of the vessel wall. Grainer et al. teach that the activators re-establish a suitable blood flow through the vessel by repeat angioplasty, atheroectomy, or coronary artery bypass surgery (pages 7 line25- page 8 line 10).

Grainger et al. do not teach the employment of the specific structural analog of tamoxifen such as idoxifene, toremifene and droloxifene and the subject population of a cardiovascular patients having diabetes.

Chander et al. that idoxifene (pyrrolidino-4-iodotomoxifen) is a new analogue of tamoxifen (see title).

Sachs et al. teach that antiestrogens such as tamoxifen and toremifene are hormonal analogs (column 6 lines 50-55).

Hasmann et al. teach that droloxifene is a new antiestrogen related to tamoxifen and found to effectively induce expression of the negative growth factor TGF-beta (abstract).

Frank teaches that the pathogenesis of diabetic retinopathy that several growth factors has been identified in the retina that may promote revascularization, however, that transforming growth-factor b (TGF-b), appears to be an important inhibitor of revascularization. (abstract).

It would have been obvious to one of ordinary skill in the art to employ a structural analogue such as idoxifene, toremifene or droloxifene for the treatment of a cardiovascular indications characterized by decreased lumen diameter by increasing

the level of TGF-beta in a mammal. One would have been motivated to make such a modification because Grainger et al. teach that tamoxifen as well as its analogues or derivatives thereof are a preferred TGF-beta activator/production stimulator that are useful in increasing vessel diameter in a diseased or injured vessel of a mammal that is characterized by a reduced vessel lumen diameter and because idoxifene and toremifene are the tamoxifen analogues which stimulate TGF-beta activator/production that is effective to treat a reduced vessel lumen diameter in a disease. There is a reasonable expectation of successfully treating a disease characterized by a decreased lumen vessel diameter with idoxifene, toremifene or droloxifene which are analogs of tamoxifen and the tamoxifen analogs are the preferred TGF-beta activator/production stimulators as taught by Grainger et al. With regard to administration of tamoxifen analogs to the diabetic mammal afflicted with a cardiovascular indication set forth in claims 182-194 such is obvious choice because tamoxifen analogs are effective in inducing TGF beta which are useful for the treatment of a cardiovascular indications. Moreover, that TGF-b is an important inhibitor of revascularization that is involved in the pathogenesis of diabetic retinopathy. Therefore, one of ordinary skill in the art would expect that administration of tamoxifen analogs that increase TGF-beta such as idoxifene, toremifene or droloxifene would reduce diabetic retinopathy because that TGF-beta inhibits revascularization that is involved in the pathogenesis of diabetic retinopathy.

Claims 231 and 234 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yang (U.S.Patent No. 5, 445,941) of record in view of Frank (1991).

Yang teaches that antiestrogen such as tamoxifen or toremifene secrete TGFb. (column 2, under antiestrogens, column 4, lines 6-10).

Yang does not teach the treatment of diabetic retinopathy with tamoxifen structural analogues set forth in claim 231 including toremifene and idoxifene set forth in claim 234.

Frank teaches that the pathogenesis of diabetic retinopathy that several growth factors has been identified in the retina that may promote revascularization, however, that transforming growth-factor b (TGF-b), appears to be an important inhibitor of revascularization. (abstract).

It would have been obvious to one of ordinary skill in the art to employ structural analogues of tamoxifen such as toremifene for the treatment of diabetic retinopathy because Yang teaches an analogue of tamoxifen such as toremifene secretes TGF-b and that TGF-b is an important inhibitor of revascularization that is involved in the pathogenesis of diabetic retinopathy. The cited reference discloses compounds which have a viable utility and toremifene is structural analogs of the claimed compounds. The claimed compounds set forth in claims 231 and 234 (idoxifene) are so closely related structurally to the homologous; isomeric or analogous tamoxifen and toremifene of the reference as to be structurally obvious therefrom in the absence of any unobvious or unexpected properties especially since one of ordinary skill in the art would expect that compounds so closely related structurally would have the same or essentially the

same properties. Therefore, one would have been motivated to make such a modification in order to reduce or halt the pathogenesis of diabetic retinopathy by inhibiting revascularization by employment of toremifene or a structural analogues thereof including idoxifene because one of ordinary skill in the art would reasonably also expect the compounds that are so closely related structurally would also secrete TGF-b that is an important inhibitor of revascularization as taught by Frank.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

**Response to Arguments**

Applicants' arguments filed November 4, 2010 have been fully considered but they are not persuasive. Applicants argument with regarding the nonstatutory obviousness-type double patenting rejection over the claims in U.S.Patent No. 5,847,007, that the route of administration, population to be treated, agents employ, and/or the outcome to be achieved are different. In response, claim 1 of the patent, '007 teaches a method of treatment of atherosclerosis comprising administering a dose of a therapeutic agent in an amount effective to elevate the level of TGF-beta such as

tamoxifen or structural analog to inhibit atherosclerotic lesion. The instant application teaches the method of treatment of a cardiovascular indication characterized by a decreased lumen diameter in an amount of tamoxifen analog effective to increase the level of TGF-beta elevation. One of ordinary skill in the art would immediately envision that the condition such as atherosclerosis is a cardiovascular condition characterized by decreased lumen diameter with lipid accumulation, increased plaque stability. The patent teaches selection of an agent such as tamoxifen analog. Though the patent does not explicitly teach administration of cytostatic dose, such dose is contemplated by the effective dosage claimed in the patent which elevates the level of TGF-beta by treating atherosclerosis. The route of administration is deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration. Accordingly, the rejected claims of the instant application are obvious over the claims of the patent.

With regard to 35 U.S.C. 103 rejection, Applicants argue that Grainger points out that raloxifene, which as anti-estrogenic properties and has some structural similarities to tamoxifen does not elevate TGF-beta 1 levels. This is not persuasive because raloxifene having the effect of increasing TGF-beta expression is well known in view of May (U.S.Patent No. 5,552,415, see abstract, claims 1-4). Therefore, it would have been obvious to one of ordinary skill in the art to employ a structural analogue such as idoxifene or toremifene for the treatment of a cardiovascular indications characterized by decreased lumen diameter by increasing the level of TGF-beta in a mammal. One would have been motivated to make such a modification because Grainger et al. teach

that tamoxifen as well as its analogues or derivatives thereof are a preferred TGF-beta activator/production stimulator that are useful in increasing vessel diameter in a diseased or injured vessel of a mammal that is characterized by a reduced vessel lumen diameter and because idoxifene and toremifene are the tamoxifen analogues which stimulate TGF-beta activator/production that is effective to treat a reduced vessel lumen diameter in a disease. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

## Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JENNIFER M. KIM whose telephone number is (571)272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 571-272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JENNIFER M KIM/
Primary Examiner, Art Unit 1628

Jmk
January 13, 2011